better NHS; and that would mean a more expensive NHS. Even the DHSS admits[12] that "without more resources or more intensive use of those that exist there must be considerable doubt about whether those parts of the acute sector most affected by demographic change will be able to meet the demands made on them." More money has to be found if the service is not to continue to decline; some of that money must be earmarked for expanding the consultant grades.

Unfilled consultant vacancies reflect the unattractiveness of the prospects in many hospitals. Junior hospital doctors may be able to face the prospect of two or three years working in oppressive, unsatisfactory surroundings. Even with medical unemployment potential consultants will be less inclined to commit themselves for life unless the whole package—job satisfaction, life style, and pay—is acceptable. The Social Services Committee has recommended that consultants should not have a "work-sensitive" contract. They must, however, be given some confidence in their future if they are to agree to the new balance in the hospital service.

[1] Scottish Committee for Hospital Medical Services. *Medical education and hospital career structure*. Edinburgh: British Medical Association, 1954. (Hamilton Report.)

[2] Ministry of Health/Department of Health for Scotland. *Report of the Joint Working Party on the Medical Staffing Structure in the Hospital Service*. London: HMSO, 1961. (Platt Report.)

[3] Scottish Home and Health Department. *Medical staffing structure in Scottish hospitals*. London: HMSO, 1964. (Wright Report.)

[4] Department of Health and Social Security/Department of Health for Scotland. *Report of the Working Party on the Responsibilities of the Consultant Grade*. London: HMSO, 1969. (Godber Report.)

[5] King Edward's Fund for London Working Party. *The organisation of hospital clinical work*. London: King's Fund Centre, 1979.

[6] Health Departments/Joint Consultants Committee. Hospital staffing structure (medical and dental). 1st progress report, *Br Med J* 1969;iv, suppl:53-6; 2nd progress report, 1971;iii, suppl:119-21; 3rd progress report, 1972;iii, suppl: 143-6.

[7] Anonymous. Medical manpower, staffing, and training requirements. Report of a BMA Council working party. *Br Med J* 1979;i:1365-74.

[8] Hospital Staffing Subcommittee. The future pattern of hospital staffing. Ascot: Hospital Consultants and Specialists Association, 1979. (Morrison Report.)

[9] Joint Consultants Committee. *Hospital staffing in the '80s*. London: Joint Consultants Committee, 1980. (Nabarro Report.)

[10] Social Services Committee. *Fourth report. Medical education with special reference to the number of doctors and the career structure in hospitals*. London: HMSO, 1981. (Short Report.)

[11] Butler JR. Scottish paradox: more doctors, worse health? *Br Med J* 1979; ii:809-10.

[12] Department of Health and Social Security. *Report of a study of the acute hospital sector*. London: HMSO, 1981.

Regular Review

Pathogenesis and treatment of myasthenia gravis

GLENIS K SCADDING, C W H HAVARD

Myasthenia gravis has an incidence of about 1 in 30 000, so it is not a common disease—but it is important, for two reasons. Firstly, awareness of the disease will encourage early diagnosis any may prevent months or even years of misdiagnosis. The average time taken to make the diagnosis is two years: when the muscle weakness affects limb girdles, distal limbs, and trunk muscles there may be no physical signs, and a wrong diagnosis of psychiatric illness is commonly made. Secondly, the pathogenesis of myasthenia gravis is characteristic of autoimmune disease, and, indeed, is an archetypal example.

Myasthenia gravis is a disorder of neuromuscular function due to a reduction of available acetylcholine receptors at the neuromuscular junction. Typically, the muscle weakness is worse after effort and improved by rest and has a characteristic distribution, affecting the extraocular, bulbar, neck, limb girdle, distal limb, and trunk muscles, in that order. The myasthenia responds to treatment with cholinesterase inhibitors, which prolong the action of acetylcholine at the neuromuscular junction. The quick-acting anticholinesterase edrophonium (Tensilon) provides a useful diagnostic test for myasthenia gravis. The diagnosis is not difficult so long as the possibility is kept in mind.

Two-thirds of myasthenic patients are women, with a peak age of onset in the 20s. Men tend to develop the disease later in life, and most patients presenting over the age of 50 are male. Spontaneous remissions occur in a quarter of the patients, but these rarely last more than two years and are not usually repeated. If myasthenia remains confined to the extraocular muscles for over a year the symptoms rarely become generalised. The several varieties of myasthenia gravis have different clinical, immunological, therapeutic, and HLA characteristics.[1]

Clinical patterns

Generalised myasthenia has three clinical patterns. Firstly, it may be associated with thymoma, when there is no clear HLA association. Patients have a high titre of antibodies to acetylcholine receptors and usually also have circulating antibodies to skeletal muscle. Secondly, it may be associated with thymitis in patients under the age of 40, and in this group there is an association with HLA-B8 or DRW3 or both. These patients have other associated autoimmune diseases but do not usually possess antibodies to striated muscle. Such patients do well after thymectomy. Thirdly, it may be associated with thymitis in patients over the age of 40. These patients have a high incidence of HLA-A3 and B7 or DRW2, or both. They also have the lowest titres of antibodies to acetylcholine receptors of patients with generalised myasthenia.

In ocular myasthenia the muscular weakness is confined to the extraocular muscles. Such patients do not benefit from thymectomy but usually respond to corticosteroids. They have

the lowest mean antibody titre to acetylcholine receptors, and in one-quarter the values are within the normal range.

Neonatal myasthenia is a transient form of myasthenia gravis appearing in about 12% of babies born to myasthenic mothers: it is due to the placental transfer of antibodies to acetylcholine receptors from mother to baby. Symptoms may persist for one to six weeks; the baby's strength improves as the antibody titre falls.

Congenital myasthenia constitutes a group of disorders, some of which are genetic. In some patients the defect is presynaptic; in one there was an absence of acetylcholinesterase at the end-plate. Anticholinesterase drugs are unhelpful. Immunological features are not present and antibodies to acetylcholine receptors do not occur.

Penicillamine-induced myasthenia gravis is a disorder similar to true myasthenia gravis[2] with muscular fatigability and antibodies to acetylcholine recptors. It usually occurs after some months of treatment with penicillamine and, like other autoantibody diseases induced by penicillamine, occurs in susceptible people. Thus patients with rheumatoid arthritis are much more likely to develop myasthenia gravis when treated with penicillamine than patients suffering from Wilson's disease or cystinuria. The disorder usually remits after stopping the drug, when antiacetylcholine receptor titres fall with a half life of two to three months.[3] This review is confined to generalised myasthenia gravis.

Immune aspects

The suggestion that myasthenia gravis might be an autoimmune disease came from three sources. As long ago as 1959[4] the histological appearances of the thymus in myasthenia gravis were noted to be similar to those of the thyroid in Hashimoto's disease. In 1960 the high incidence of other autoimmune phenomena in patients with myasthenia gravis led Simpson to formulate his hypothesis[5] that the disease was due to antibodies to the motor end-plate. Simultaneously fluctuations of complement levels with disease activity were reported.[6]

Circulating antibodies to striated muscle, which cross-react with thymic myoid cells, were reported in some patients with myasthenia in 1960.[7] Such antibodies are, however, present in only about one-third of patients with myasthenia gravis, and these are usually those with a tumour of the thymus. Antibodies to striated muscle may also occur in some patients with a thymic tumour who do not have myasthenia gravis and they do not play any pathogenic part in the muscular weakness. Antibodies to the motor end-plate were sought in the 1960s but were not found. Further progress resulted from the discovery of alpha-bungarotoxin (alpha-BT), a snake-venom protein which binds specifically and irreversibly to acetylcholine receptors.[8]

Next, purification of the acetylcholine receptor from the electric organ of electric eels was achieved by affinity chromatography using similar but less irreversible toxins.[9] Immunisation of rabbits with purified acetylcholine receptor emulsified in Freund's complete adjuvant resulted in their developing muscular weakness and dying of respiratory paralysis.[10] These animals were suffering from what is now called experimental autoimmune myasthenia gravis, having developed antibodies to the eel acetylcholine receptor, which cross-reacted with their own acetylcholine receptor. The similarities between the clinical and experimental findings in experimental autoimmune myasthenia gravis and myasthenia gravis prompted a renewed search for antibodies against acetylcholine receptors in the human disease. In 1974[11] a factor present in the globulin fraction of the sera of patients with myasthenia gravis which blocked binding of alpha-BT to solubilised rat acetylcholine receptors was noted. Since then several other methods have shown humoral interference with acetylcholine receptors.

The most widely used current method of measuring antibodies to acetylcholine receptors in human serum is a radioimmunoassay using as antigen radioiodinated alpha-BT bound to acetylcholine receptors in crude detergent extracts of human muscle.[12] After incubation with the test serum any immune complexes are precipitated by anti-IgG. Antibodies to acetylcholine receptors have been found in 87-93% of myasthenic patients in this fashion. Antibodies to the alpha-BT binding site are not, of course, measured by this method. Control serum from normal people or from patients with other neurological or autoimmune diseases gives results close to zero. The range of antibody titres found in myasthenia gravis is wide, and values from 0 to 840 nmol alpha-BT binding sites precipitated per litre of serum were reported in one series.[13] The antibody titre does not correspond with the severity of the disease, though patients with thymomas tend to have high titres and those with predominantly ocular symptoms have the lowest mean titres. About one-quarter of patients with ocular myasthenia have titres within the control range when leg muscle is used as the antigen; some of these become positive if ocular muscle is used instead.

Pathogenicity of antibodies to acetylcholine receptors

There is increasing evidence that the antibodies to acetylcholine receptors are important in the pathogenesis of myasthenia gravis and are not, like antibodies to striated muscle, an epiphenomenon. A decrease in the number of functioning acetylcholine receptors is sufficient to account for the signs of myasthenia. This has been shown by injecting alpha-BT into animals.[14] Several observations suggest that antibodies to acetylcholine receptors are responsible for the muscle weakness. Mice given injections of myasthenic immunoglobulin develop muscle weakness and a decreased number of acetylcholine receptors as shown by alpha-BT binding.[15] Complement C3 is necessary for this effect but not C5.[16] Plasma exchange shows that the concentration of antibodies to acetylcholine receptors rather than of C3 or total IgG has an inverse relation to muscle strength.[17] Neonatal myasthenia is associated with the presence of antibodies to acetylcholine receptors transferred transplacentally to the baby,[18] and the infant improves as the antibody level falls.[19] Thoracic duct drainage is beneficial in myasthenia gravis, and reinfusion of the cell-free lymph causes clinical deterioration.[20]

Though antibodies to acetylcholine receptors appear to cause muscle weakness, the poor correlation with severity of the disease remains unexplained. Indeed, about 5% of patients with generalised myasthenia gravis cannot be shown to have antibodies to acetylcholine receptors. Conversely, patients have been found with high titres of antibodies but in whom the myasthenia is in clinical remission. Heterogeneity of the antibodies is partly responsible for this. In any subject there are probably several types of antibodies to acetylcholine receptors, some of which are more effective at blocking or destroying acetylcholine receptors than others. In theory antibodies to the alpha-BT binding sites would cause a profound decrease in neuromuscular transmission and yet would not be detected by the routine radioimmunoassay. Alternatively, detergent

extraction of the acetylcholine receptors may destroy or hide antigenic sites. The severity of muscular weakness will also be determined by the turnover of acetylcholine receptors. The rates of resynthesis of acetylcholine receptors probably vary among subjects. In a few patients humoral factors may not be concerned and damage to acetylcholine receptors could be cell mediated, though there is little morphological evidence of this in myasthenia gravis.

How do antibodies to acetylcholine receptors cause muscle weakness?

Three mechanisms could account for the effect of antibodies to acetylcholine receptors on neuromuscular transmission.

Firstly, the effect could be due to complement-mediated lysis. IgG has been shown on the postsynaptic membrane and its distribution follows that of acetylcholine receptors. C3 is also present in the postsynaptic membrane, together with a little C9, which is the lytic component of complement.[21] The latter is found mainly on debris in the synaptic space. This is consistent with complement-mediated lysis of the postsynaptic membrane leading to both loss of acetylcholine receptors and the characteristic morphological changes—elongation and simplification of the postsynaptic membrane and widening of the synaptic cleft.

Secondly, the effect could be due to modulation. Acetylcholine receptors are normally degraded and new ones synthesised; however, the rate of degradation is increased after cross-linking of acetylcholine receptors by antibody.[22] In some people resynthesis may also increase,[23] and the balance between the two processes will determine the number of acetylcholine receptors remaining.

Thirdly, direct blocking of the acetylcholine-binding site by antibodies to acetylcholine receptors binding at or near the site is a theoretical possibility. Binding of alpha-BT to human acetylcholine receptors is blocked by serum from one-third of patients with myasthenia gravis,[24] showing that such antibodies exist, but as yet few reports have appeared of a direct effect on a neuromuscular preparation[25 26] of serum from patients with myasthenia gravis. In contrast, complement-depleted sera from animals with experimental animal myasthenia gravis do have a direct effect on neuromuscular preparations, and the time course and lack of dependence on temperature suggest that this is due to a direct block of acetylcholine-receptor function rather than an increase in acetylcholine-receptor degradation.[27 28]

Role of the thymus

The thymus is a central lymphoid organ responsible for the maturation of T lymphocytes. These are not antibody-producing cells but serve a variety of functions such as helper cells, suppressor cells, and cytotoxic T cells. B cells, which are precursors of the antibody-producing plasma cells, are rare in the normal thymus.

That the thymus plays a part in myasthenia gravis is suggested by the histological appearances of the gland and the effect of thymectomy on the course of the disorder. Between 10% and 15% of myasthenic patients have a thymoma, and over two-thirds of the remainder show "thymitis,"[29] which is an infiltration of the thymic medulla with lymphocytes forming follicles with germinal centres in which there are B cells. Thymectomy results in remission or improvement in 60-80% of patients, though the delay before improvement occurs varies considerably and may be several years.[30]

Recently we have shown that the thymus is an active site of production of antibodies to acetylcholine receptors in most patients with thymitis, though it cannot account for all the circulating antibodies to acetylcholine receptors. None of the seven thymomas studied synthesised antibodies to acetylcholine receptors in vitro, but the ratio of antiacetylcholine receptors to total IgG was higher in thymic tissue than in peripheral blood, suggesting synthesis in vitro or accumulation.[31] Irradiated thymic cells, which are viable but incapable of antibody synthesis, augment the production of antibodies to acetylcholine receptors by autologous peripheral blood lymphocytes, suggesting that the thymus is the site of some factor, possibly a helper T cell, which enhances synthesis of acetylcholine receptors.[32]

The thymus might also be the source of the original acetylcholine receptors to which tolerance is broken, possibly as a result of viral infection. Acetylcholine receptors have been found on muscle-like cells cultured from thymuses.[33] Possibly in myasthenia gravis there may be a stage of proliferation of these cells with acetylcholine receptors on their surface within the thymus. T cells might then become sensitised to these thymic cells and cause B cells to synthesise antibodies to acetylcholine receptors which cross-react with skeletal muscle.[34] Both stages could be subject to genetic control.

Medical treatment

Symptomatic treatment is by anticholinesterase drugs, which prolong the action of acetylcholine at the postsynaptic membrane. Pyridostigmine, the drug most commonly used, is given by mouth, and is effective for three to four hours. The usual starting dose is 60 mg four times a day, and this is increased until the maximum response is obtained. Neostigmine has a shorter duration of action but a quicker onset and can be useful at the start of the day for this reason. The dose of anticholinesterase that gives the maximum therapeutic response must be established. This may not restore muscle strength to normal, and patients often have to live with some degree of disability. If the dose of drugs is increased above the maximum response level in the forlorn hope of improving physical activity the opposite effect will be produced, with progressive muscle weakness possibly ending in a cholinergic crisis.

Like any other people, patients with myasthenia are subject to the fatigue of mental and physical strain, and they need to be warned not to increase the dose of medication to counter such physiological fatigue. Intravenous edrophonium 5-10 mg may be used in between doses to decide whether the patient is having too much or too little anticholinesterase. It is important to inject 2 mg initially and then pause before administering the remainder in case the patient is already overdosed. Not uncommonly, the transitory increase in anticholinesterase renders some muscles stronger and others weaker. Since the respiratory and bulbar muscles are the most important they should receive the optimum treatment. Anticholinesterases potentiate the action of acetylcholine at muscarinic as well as nicotinic acetylcholine receptors; hence they can cause abdominal colic, diarrhoea, small pupils, lachrymation, and salivation. These side effects act as useful indicators of overdosage and so atropine should not be routinely prescribed to prevent them. Absorption of pyridostigmine from the gut is very variable.[35] Pyridostigmine cannot be given parenterally.

Neostigmine may, however, be given intramuscularly or subcutaneously through an infusion pump.[36]

Immunosuppression—The main groups of immunosuppressive drugs used in myasthenia gravis are corticosteroids and azathioprine. The place of steroids in myasthenia gravis is for patients who are insufficiently improved after thymectomy or who are seriously ill before it. They are also useful in patients with ocular myasthenia gravis and occasionally in patients who are unsuitable for thymectomy. Their mode of action in autoimmune disease is uncertain. Possibly corticosteroids exert some of their therapeutic effect directly at the neuromuscular junction. They appear to cause a reduction in antibodies to acetylcholine receptors. The improvement after steroids (about 1 mg/kg on alternate days) may take several weeks to become manifest. Initial deterioration is often found during steroid treatment, possibly because the effectiveness of anticholinesterases is enhanced, provoking a cholinergic crisis. This deterioration may be kept to a minimum if the initial dose of steriods is low and increased gradually and also if the dose of anticholinesterase is decreased when treatment with corticosteroids is begun. Steroid treatment is best started on an inpatient basis and under close supervision by a physician used to dealing with myasthenia gravis.

Azathioprine (2·5 mg/kg/day) is also effective in causing clinical improvement and reducing antibodies to acetylcholine receptors. These effects occur more slowly than with steroids: improvement starts in six to 12 weeks and becomes maximal at six to 15 months. The results of treating 78 patients with azathioprine over 11 years have recently been reported.[37] Of these patients, 31 are in complete remission, 40 much improved, and none is worse. No relapse has occurred in patients receiving more than 150 mg daily, whereas two of 12 taking 100 mg daily and 10 of 18 taking less than 50 mg daily have relapsed. In eight patients in complete remission azathioprine has been stopped for six months to three and a half years without relapse. The response to treatment with azathioprine[38] is more likely to be favourable in men, over the age of 35, after a duration of illness of less than 10 years, in the absence of HLA-B8, when there is histological evidence of a thymoma or hyperplasia, and when a high titre of antibodies to acetylcholine receptors is found. Since azathioprine causes bone marrow depression regular blood counts are mandatory. It is probably teratogenic and should be avoided if possible in women who may become pregnant—though normal children were born to all of nine mothers receiving azathioprine for autoimmune disorders.[39] Azathioprine should be reserved for patients with severe disease not responding to other forms of treatment; it is also indicated in association with plasma exchange to prevent the rebound hypersecretion of antibody.

Plasma exchange was first used in myasthenia gravis in 1976[10] and can, like thoracic-duct drainage, produce a dramatic though short-lived improvement in muscular strength associated with a fall in antibodies to acetylcholine receptors. In myasthenia gravis it should be used to improve severely ill patients while other forms of treatment become effective. Long-term plasma exchange and immunosuppression does not confer greater benefit than immunosuppression alone.[41]

Surgical treatment

Thymectomy has become increasingly important in managing patients with myasthenia gravis. A retrospective comparison of medical (without steroids) versus surgical treatment in matched pairs of patients with myasthenia gravis showed that patients treated by thymectomy were more likely to achieve complete remission and less likely to die from their disease.[42] The risks of thymectomy are now small, provided the operation is undertaken in a centre with good facilities for intensive care and in a unit with experience of the operation. The operation should be performed transsternally, since the entire thymus must be removed, including the small islets of cells lying in mediastinal fat—otherwise regrowth of the thymus may lead to deterioration in the myasthenia.[43] The incidence of remission increases with the number of years after thymectomy.[30] Complete remission or improvement may be expected in 80% of patients without a tumour of the thymus, though three to five years may elapse before the benefits of operation are apparent. In patients with tumours either surgical excision or radiotherapy may be used to prevent local spread, but the prognosis is worse.

The explanation of the beneficial effects of thymectomy is uncertain. Though the titres of antibodies to acetylcholine receptors probably fall after thymectomy, there is no generalised impairment of antibody production after the operation[44] and no evidence that thymectomy is immunosuppressive.[45]

Deteriorating myasthenia gravis

Myasthenia may worsen because of a natural deterioration in the disease, but several external factors may be responsible. A change in hormonal state, such as menstruation or pregnancy, worsens the disorder in some women, and thyrotoxicosis frequently provokes deterioration. Some drugs may aggravate myasthenia. Drugs such as bulk laxatives may reduce the absorption of pyridostigmine. Myasthenic patients are obviously much more sensitive to the neuromuscular blocking drugs. Antiarrhythmic drugs reduce the excitability of muscle membrane and probably also inhibit neuromuscular transmission so that quinine, quinidine, procainamide, lignocaine, and propranolol should be avoided. Tonic water contains quinine, and this may be enough to upset a patient with myasthenia. Antibiotics of the aminoglycoside group impair neuromuscular conduction by inhibiting the release of acetylcholine, so that streptomycin, gentamicin, kanamycin, neomycin, and polymyxin should be avoided. Patients with myasthenia are sensitive to the central nervous system depressants: drugs such as morphine and barbiturates must be used with caution. Diuretics can aggravate myasthenia if they produce hypokalaemia. Overdosage with anticholinesterases will also cause increased muscular weakness. Intercurrent infection and surgery may be the cause of deterioration.

Deterioration in a patient's condition may result in crisis with respiratory failure and virtual paralysis. This may be myasthenic or cholinergic, and both are dangerous. The treatment is intubation and ventilation with all treatment stopped. After 24 to 48 hours anticholinesterase drugs should be restarted and corticosteroid treatment or plasma exchange may be indicated if the response to anticholinesterase drugs is unsatisfactory.

Alternative forms of treatment

Most alternative forms of treatment are non-specific and have been tried only in patients refractory to everything else. Low doses of total-body irradiation have been used to decrease circulating lymphocytes.[46] Antithymocyte globulin has been used to decrease thymic lymphocytes.[47] Eight out of 10 patients

tested showed some response to this after thymectomy; the two patients who had refused thymectomy did not respond. A specific measure which may hold promise for treatment of human myasthenia gravis is anti-iodiotype antibodies. These are antibodies to antibodies and are specific for that part of the antibody which is unique by virtue of its affinity for antigen. Anti-idiotypes specific for human antibodies to acetylcholine receptors could prove to be of value in the acute condition, and might also be able to restore normal control mechanisms.[48] Nevertheless, anti-idiotype antibodies to human acetylcholine receptors will be complicated and difficult to produce. There is also a theoretical risk of increasing production of antibodies to acetylcholine receptors by inhibition of suppressor T cells.

GLENIS K SCADDING
Wellcome research fellow

C W H HAVARD
Consultant physician and endocrinologist

Royal Free Hospital,
London NW3 2QG

[1] Compston DAS, Vincent A, Newsom-Davis J, Batchelor JR. Clinical, pathological, HLA antigen and immunological evidence for disease heterogeneity in myasthenia gravis. *Brain* 1980;**103**:579-601.
[2] Bucknall RC, Dixon AStJ, Glick EN, Woodland J, Zutshi DW. Myasthenia gravis associated with penicillamine treatment for rheumatoid arthritis. *Br Med J* 1975;i:600-2.
[3] Vincent A, Newsom-Davis J, Martin V. Anti-acetylcholine receptor antibodies in D-penicillamine-associated myasthenia gravis. *Lancet* 1978;i:1254.
[4] Smithers DW. Tumours of the thyroid gland in relation to some general concepts of neoplasia. *Journal of the Faculty of Radiologists* 1959;**10**:3-16.
[5] Simpson JA. Myasthenia gravis. A new hypothesis. *Scott Med J* 1960;**5**:419-36.
[6] Nastuk WL, Plescia OJ, Osserman KE. Changes in serum complement activity in patients with myasthenia gravis. *Proc Soc Exp Biol Med* 1960;**105**:177-84.
[7] Strauss AJL, Seegal BC, Hsu KC, Burkholer PM, Nastuk WL, Osserman KE. Immunofluorescence demonstration of a muscle binding complement-fixing serum globulin fraction in myasthenia gravis. *Proc Soc Exp Biol* 1960;**105**:184-91.
[8] Chang CC, Lee CY. Isolation of neurotoxins from the venom of Bungarus multicinctus and their modes of neuromuscular blocking action. *Arch Int Pharmocodyn Ther* 1963;**144**:241-57.
[9] Fulpius BW. Characterisation, isolation and purification of cholinergic receptors. In: Thesleff S, ed. *Motor innervation of muscle*. London: Academic Press, 1976:1-29.
[10] Patrick J, Lindstrom J. Autoimmune response to acetylcholine receptor. *Science* 1973;**180**:871-2.
[11] Almon RR, Andrew CG, Appel SH. Serum globulin in myasthenia gravis: inhibition of α-bungarotoxin binding to acetylcholine receptors. *Science* 1974;**186**:55-7.
[12] Lindstrom J. An assay for antibodies to human acetylcholine receptor in serum from patients with myasthenia gravis. *Clin Immunol Immunopathol* 1977;**7**:36-43.
[13] Lindstrom JM, Seybold ME, Lennon VA, Whittingham S, Duane DD. Antibody to acetylcholine receptor in myasthenia gravis: prevalence, clinical correlates and diagnostic value. *Neurology* 1976;**26**:1054-9.
[14] Takamori M, Iwanaga S. Experimental myasthenia due to alpha-bungarotoxin. *Neurology* 1976;**26**:844-8.
[15] Toyka KV, Drachman DB, Pestronk KA, Kao I. Myasthenia gravis: passive transfer from man to mouse. *Science* 1975;**190**:397-9.
[16] Toyka KV, Drachman DB, Griffin DE, *et al*. Myasthenia gravis: study of humoral immune mechanisms by passive transfer to mice. *N Engl J Med* 1977;**296**:125-31.
[17] Newsom-Davis J, Pinching AJ, Vincent A, Wilson SG. Function of circulating antibody to acetylcholine receptor in myasthenia gravis: investigated by plasma exchange. *Neurology* 1978;**28**:266-72.
[18] Keesey J, Lindstrom J, Cokely H, Herrman C. Anti-acetylcholine receptor antibody in neonatal myasthenia gravis. *N Engl J Med* 1977;**296**:55.
[19] Vincent A, Newsom-Davis J, Martin V. Anti-acetylcholine receptor antibodies in D-penicillamine-associated myasthenia gravis. *Lancet* 1978;i:1254.
[20] Bergström K, Franksson C, Matell G, von Reis G. The effect of thoracic duct lymph drainage in myasthenia gravis. *Eur Neurol* 1973;**9**:157-67.
[21] Engel AG, Sahashi K, Lambert EH, Howard FM. The ultra structural localisation of the acetylcholine receptor, immunoglobulin G and the third and ninth complement components at the motor end plate and implications for the pathogenesis of myasthenia gravis. *Proceedings of 4th International Congress on Neuromuscular Diseases 1978*. Amsterdam: Excerpta Medica Foundation, 1979:111-22. (International Congress Series, No 455.)
[22] Drachman DB, Angus CW, Adams RN, Michelson JD, Hoffman GJ. Myasthenic antibodies cross-link acetylcholine receptors to accelerate degradation. *N Engl J Med* 1978;**298**:1116-22.
[23] Wilson SG, Vincent A, Newsom-Davis J. Effect of human myasthenic immunoglobulin G on mouse acetylcholine receptor. *Clin Sci* 1980;**57**:20p.
[24] Vincent A, Newsom-Davis J. α-Bungarotoxin and anti-acetylcholine receptor antibody binding to human acetylcholine receptor. In: Ceccarelli B, Clementi F, eds. *Advances in cytopharmacology*. Vol 30. *Neurotoxins—tools in neurobiology*. New York: Raven Press, 1976:267-78.
[25] Shibuya N, Mori K, Nakazawa Y. Serum factor blocks neuromuscular transmission in myasthenia gravis: electrophysiologic study with intracellular microelectrodes. *Neurology* 1978;**28**:804-11.
[26] Ito Y, Miledi R, Molenaar PC, Newsom-Davis J, Polak RL, Vincent A. Neuromuscular transmission in myasthenia gravis and the significance of anti-acetylcholine receptor antibodies. In: Lunt GG, Marchbanks RM, eds. *Biochemistry of myasthenia gravis and muscular dystrophy*. London: Academic Press, 1978:89-110.
[27] Berti F, Clementi F, Conti-Tronconi B, Folco GC. A cholinoceptor antiserum; its pharmacological properties. *Br J Pharmacol* 1976;**57**:17-22.
[28] Green DPL, Miledi R, Vincent A, Neuromuscular transmission after immunization against acetylcholine receptors. *Proc R Soc Lond (Biol)* 1975;**189**:57-68.
[29] Castleman B, Norris EH. The pathology of the thymus in myasthenia gravis. A study of 35 cases. *Medicine* 1949;**28**:27-58.
[30] Papatestas AE, Genkins G, Horowitz SH, Kornfeld P. Thymectomy in myasthenia gravis: pathologic, clinical and electrophysiologic correlations. *Ann NY Acad Sci* 1976;**274**:555-73.
[31] Scadding GK, Newsom-Davis J, Vincent A, Henry K. Synthesis of acetylcholine receptor antibodies by thymic lymphocytes in vitro. Correlation with thymic histology. *Neurology* (in press).
[32] Newsom-Davis J, Willcox N, Scadding GK, Calder L, Vincent A. Anti-acetylcholine receptor antibody synthesis by cultured lymphocytes in myasthenia gravis: thymic and peripheral blood cell interactions. *Proceedings of New York Academy of Sciences conference on myasthenia, December 1980*. (In press.)
[33] Kao I, Drachman DB. Thymic muscle cells bear acetylcholine receptors: possible relation to myasthenia gravis. *Science* 1977;**195**:74-5.
[34] Wekerle H, Ketelson U-P. Intrathymic pathogenesis and dual genetic control of myasthenia gravis. *Lancet* 1977;i:678-80.
[35] White MC, De Silva P, Havard CWH. Plasma pyridostigmine levels in myasthenia gravis. *Neurology* 1981;**31**:145.
[36] Bingle JP, Rutherford JD, Woodrow P. Continuous subcutaneous neostigmine in the management of severe myasthenia gravis. *Br Med J* 1979;i:1050.
[37] Hertel G, Reuther P, Mertens HG. Effect of immunosuppressive drugs (azathioprine). *Proceedings of New York Academy of Sciences conference on myasthenia gravis, December 1980*. (In press.)
[38] Matell G, Mackay IR, Lambert RP. Effect of immunosuppressive drugs (azathioprine). *Proceedings of New York Academy of Sciences conference on myasthenia gravis, December 1980*. (In press.)
[39] Symington GR. Cancer and teratogenesis: infrequent occurrence after medical use of immunosuppressive drugs. *Aust NZ J Med* 1977;**7**:368-72.
[40] Pinching AJ, Peters DK, Newsom-Davis J. Remission of myasthenia gravis following plasma-exchange. *Lancet* 1976;ii:1373-6.
[41] Newsom-Davis J, Wilson SG, Vincent A, Ward CD. Long-term effects of repeated plasma exchange in myasthenia gravis. *Lancet* 1979;i:464-8.
[42] Buckingham JM, Howard FM, Bernatz PE, *et al*. The value of thymectomy in myasthenia gravis: a computer-assisted matched study. *Ann Surg* 1976;**184**:453-5.
[43] Stump WJ, Adornato BT, Engel WK, McIntosh CL, Castlemano BJ. Thymectomy in myasthenia gravis. *Neurology* 1978;**28**:372-3.
[44] Scadding GK, Webster ADB, Ross M, Thomas HC, Havard CWH. Humoral immunity before and after thymectomy in myasthenia gravis. *Neurology* 1979;**29**:502-6.
[45] Scadding GK, Thomas HC, Havard CWH. The immunological effects of thymectomy in myasthenia gravis. *Clin Exp Immunol* 1979;**36**:205-23.
[46] King-Engel W, Dalakas MC, Lichter AS. Effect of splenic radiation. *Proceedings of New York Academy of Sciences conference on myasthenia gravis, December 1980*. (In press.)
[47] Pirofsky B. Effect of antithymocyte antiserum. *Proceedings of New York Academy of Sciences conference on myasthenia gravis, December 1980*. (In press.)
[48] Jerne NK. Towards a network theory of the immune system. *Ann Immunol (Paris)* 1974;**125c**:373-89.